CANCER FACTS
National Cancer Institute • National Institutes of Health

Questions and Answers About the Study of Tamoxifen and Raloxifene (STAR)

1. What is the Study of Tamoxifen and Raloxifene (STAR)?

The Study of Tamoxifen and Raloxifene (STAR) is a clinical trial (a research study conducted with people) designed to see how the drug raloxifene (Evista®) compares with the drug tamoxifen (Nolvadex®) in reducing the incidence of breast cancer in women who are at an increased risk of developing the disease. Researchers with the National Surgical Adjuvant Breast and Bowel Project (NSABP) are conducting the study at more than 400 centers across the United States, Puerto Rico, and Canada. The study is primarily funded by the National Cancer Institute (NCI), the U.S. Government's main agency for cancer research.

2. What is tamoxifen?

Tamoxifen is a drug, taken by mouth as a pill. It has been used for more than 20 years to treat patients with breast cancer. Tamoxifen works against breast cancer, in part, by interfering with the activity of estrogen, a female hormone that promotes the growth of breast cancer cells. In October 1998, the U.S. Food and Drug Administration (FDA) approved tamoxifen to reduce the incidence of breast cancer in women at high risk of the disease based on the results of the Breast Cancer Prevention Trial (BCPT). The BCPT is a study of more than 13,000 pre- and postmenopausal high-risk women ages 35 and older who took either tamoxifen or a placebo (an inactive pill that looked like tamoxifen) for up to 5 years. NSABP conducted the BCPT, which also showed that tamoxifen works like estrogen to preserve bone strength, decreasing fractures of the hip, wrist, and spine in the women who took the drug.

3. What is raloxifene?

Raloxifene is a drug, taken by mouth as a pill. In December 1997, it was approved by the FDA for the prevention of osteoporosis in postmenopausal women. Raloxifene is being studied because large studies testing its effectiveness against osteoporosis have shown that women taking the drug developed fewer breast cancers than women taking a placebo.

4. Who is eligible to participate in STAR?

Women at increased risk for developing breast cancer, who have gone through menopause and are at least 35 years old, can participate in STAR. All women must have an increased risk of breast cancer equivalent to or greater than that of an average 60- to 64-year-old woman. At that age, about 17 of every 1,000 women are expected to develop breast cancer within 5 years.

5. Why can't premenopausal women participate in STAR?

STAR is limited to postmenopausal women because the drug raloxifene has yet to be adequately tested for long-term safety in premenopausal women. NCI recently launched a separate study to evaluate the safety of raloxifene in premenopausal woman.

6. What factors are used to determine increased risk of breast cancer for the participants?

Increased risk of breast cancer is determined in one of two ways. The risk for most women is determined by a computer calculation based on the following factors:

- Current age;
- Number of first-degree relatives (mother, daughters, or sisters) diagnosed with breast cancer;
- Whether a woman had any children and her age at her first delivery;
- The number of breast biopsies a woman has had, especially if the tissue showed a condition known as atypical hyperplasia; and
- The woman's age at her first menstrual period.

Women diagnosed as having lobular carcinoma in situ (LCIS), a condition that is not cancer but indicates an increased chance of developing invasive breast cancer, are eligible based on that diagnosis alone, as long as any treatment for the condition was limited to local excision. Mastectomy, radiation, or systemic therapy would disqualify a woman with LCIS from the study.

7. How will a potential participant's risk of breast cancer be determined?

Each potential participant will complete a one-page questionnaire (risk assessment form), which will be forwarded to NSABP by the local STAR clinical staff. The NSABP will use computer software to generate an individualized risk profile based on the information provided and will return the profile to the local STAR site so that it can be given to the potential participant. The profile will estimate the woman's chance of developing breast cancer over the next 5 years and will also present the potential risks and benefits of the

study drugs. The woman can then use this information to help her decide whether or not she is interested in participating in STAR.

8. What other factors affect eligibility for the study?

Certain existing health conditions affect eligibility for the study. Health professionals at the STAR site will discuss these with each potential participant. For example, women with a history of cancer (except basal or squamous cell skin cancer), blood clots, stroke, or certain types of heartbeat irregularities cannot participate. Women whose high blood pressure or diabetes is not controlled also cannot participate.

Also, women taking hormone replacement therapy (estrogen or an estrogen/progesterone combination) cannot take part in the trial unless they stop taking this medication. Those who stop taking these hormones are eligible for the study 3 months after they discontinue the drugs. Women who have taken tamoxifen or raloxifene for no more than 3 months are eligible for the study, but they must also stop the medication for 3 months before joining STAR.

9. What are the common side effects of tamoxifen and raloxifene?

Like most medications, including over-the-counter medications, prescription drugs, or drugs in clinical trials, tamoxifen and raloxifene cause adverse effects in some women. The effects experienced most often by women taking either drug are hot flashes and vaginal symptoms, including discharge, dryness, or itching. It is possible that some women may experience leg cramps, constipation, pain with intercourse, sinus irritation or infection, or problems controlling the bladder upon exertion. Treatments that may minimize or eliminate most of these side effects will be available to the participants.

10. Does tamoxifen have any serious side effects?

The best information available about the serious side effects of tamoxifen comes from 30 years of clinical trials, including the BCPT. In the BCPT, women taking tamoxifen had more than twice the chance of developing endometrial cancer (cancer of the lining of the uterus or womb) compared with women who took the placebo (36 of the 6,600 women taking tamoxifen versus 15 of the 6,600 women taking placebo). The risk was higher in women over the age of 50. The increased risk is in the same range as the risk for postmenopausal women taking single-agent estrogen replacement therapy. Like all cancers, endometrial cancer is potentially life-threatening. Women who have had a hysterectomy (surgery to remove the uterus) are not at risk for endometrial cancer.

Women taking tamoxifen in the BCPT had three times the chance of developing a pulmonary embolism (blood clot in the lung) as women who took the placebo (18 women taking tamoxifen versus 6 on placebo). Three women taking tamoxifen died from these embolisms. Women in the tamoxifen group were also more likely to have a deep vein thrombosis (a blood clot in a major vein) than women on placebo (35 women

on tamoxifen versus 22 on placebo). Women taking tamoxifen also appeared to have an increased chance of stroke (38 women on tamoxifen versus 24 on placebo).

11. Does raloxifene have any serious side effects?

Information about raloxifene is limited compared with the data available on tamoxifen because of the shorter time it has been studied (about 5 years) and the smaller number of women who have been studied. Studies of raloxifene have generally involved women who received the drug to determine its effect on osteoporosis, and the duration of both therapy and followup have been short. Women taking raloxifene in clinical trials have about three times the chance of developing a deep vein thrombosis or pulmonary embolism as women on a placebo. In osteoporosis studies of raloxifene, the drug did not increase the risk of endometrial cancer. An important part of STAR will be to assess the long-term safety of raloxifene versus tamoxifen in women at increased risk of breast cancer.

12. Who will get which drug?

Participants in STAR will be randomized (assigned by chance) to receive either tamoxifen or raloxifene. In a process known as "double blinding", neither the participant nor her physician will know which pill she is receiving. Setting up a study in this way allows the researchers to directly compare the true benefits and side effects of each drug without the influence of other factors. All women in the study will take two pills a day for 5 years: half will take active tamoxifen and a raloxifene placebo (an inactive pill that looks like raloxifene); the other half will take active raloxifene and a tamoxifen placebo (an inactive pill that looks like tamoxifen). All women will receive one of the active drugs; no one in STAR will receive only the placebo. The dosages are 20 mg of tamoxifen and 60 mg raloxifene.

13. Why does everyone have to take two pills?

Tamoxifen and raloxifene have different shapes. The trial would not be double blinded if participants or physicians could tell which drug they were receiving because of its shape. The maker of tamoxifen, Zeneca Pharmaceuticals in Wilmington, Delaware, and the maker of raloxifene, Eli Lilly and Company in Indianapolis, Indiana, are providing the active pills and the look-alike placebos without charge.

14. Are participants required to have any medical exams? Who will pay for these exams?

Participants are required to have blood tests, a mammogram, a breast exam, and a gynecologic exam before they are accepted into the study. These tests will be repeated at intervals during the trial. Physicians' fees and the costs of medical tests will be charged to the participant in the same fashion as if she were not part of the trial; however, the costs for these tests generally are covered by insurance. Every effort is made to contain

the costs specifically associated with participation in this trial, and financial assistance is available for some women.

15. How can a woman enroll in the trial?

Postmenopausal women who are interested in participating in STAR should contact the center nearest to them. To locate the nearest center in the United States (including Puerto Rico) by phone, a woman can call the NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237). The number for deaf and hard of hearing callers with TTY equipment is 1–800–332–8615.

In Canada, participating centers can be located by calling the Canadian Cancer Society's Cancer Information Service at 1–888–939–3333.

To locate the nearest STAR center, visit NSABP's Web site at http://www.nsabp.pitt.edu or NCI's clinical trials Web site at http://cancertrials.nci.nih.gov on the Internet.

16. How is the safety of participants ensured? Is the trial monitored?

The safety of participants is of primary importance to STAR investigators. There are strict requirements about who can join the trial as well as frequent monitoring of participants' health status. An independent Data Safety and Monitoring Committee (DSMC) will provide oversight of the trial. The DSMC includes medical and cancer specialists, biostatisticians, and bioethicists who have no other connection to NSABP. The DSMC will meet semiannually and review unblinded data from all participants. Two other committees will also provide oversight. The Participant Advisory Board (PAB) is made up of 16 women from the BCPT. As women join STAR, board membership will change to include STAR participants. The PAB meets semiannually with professionals from NSABP and NCI and provides feedback on many study-related functions such as informed consent, participant recruitment, and communications issues. The STAR Steering Committee is made up of NSABP investigators, breast cancer advocates, experts from other medical disciplines, as well as NCI and NSABP personnel. The committee, which also meets semiannually, is charged with providing overall administrative oversight of the trial.

In addition, NSABP provides the FDA, NCI, Zeneca Pharmaceuticals, and Eli Lilly and Company with annual reports on STAR that summarize the overall data collected to date (only the DSMC receives unblinded data).

17. What is the National Surgical Adjuvant Breast and Bowel Project?

The NSABP is a cooperative group with a 40-year history of designing and conducting clinical trials, the results of which have changed the way breast cancer is treated and, now, prevented. Results of clinical trials conducted by NSABP researchers have been the dominant force in altering the standard surgical treatment of breast cancer from radical mastectomy to lumpectomy plus radiation. This group was also the first to demonstrate

that adjuvant therapy could alter the natural history of breast cancer, thus increasing survival rates.

# # #

Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online

Internet

Use http://www.cancer.gov to reach NCI's Web site.

CancerMail Service

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service

Dial 301–402–5874 and listen to recorded instructions.

This fact sheet was reviewed on 6/17/99